BK

CORRECTED VERSION *

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 31/55 — A3

(11) International Publication Number: WO 93/00094

(43) International Publication Date: 7 January 1993 (07.01.93)

(21) International Application Number: PCT/GB92/01083

(22) International Filing Date: 17 June 1992 (17.06.92)

(30) Priority data:
9113379.3 — 21 June 1991 (21.06.91) — GB
9113377.7 — 21 June 1991 (21.06.91) — GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)* : WARD, John, Gerard [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). YOUNG, Rodney, Christopher [GB/GB]; SmithKline Beecham Pharmaceuticals, The Fryth, Welwyn, Hertfordshire AL 6 9AR (GB). KAUMANN, Alberto, Julio [AR/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB).

(74) Agents: FLORENCE, Julia, A. et al.; Corporate Patents, SmithKline Beecham, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).

(81) Designated States: AU, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report: 4 March 1993 (04.03.93)

(54) Title: USE OF TETRAHYDROBENZAZEPINE DERIVATIVES FOR THE TREATMENT OF PORTAL HYPERTENSION AND MIGRAINE

(57) Abstract

Tetrahydrobenzazepine derivatives are disclosed as medicaments.

* (Referred to in PCT Gazette No.06/1993, Section II)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**FI**	Finland	**MN**	Mongolia
AU	Australia	**FR**	France	**MR**	Mauritania
BB	Barbados	**GA**	Gabon	**MW**	Malawi
BE	Belgium	**GB**	United Kingdom	**NL**	Netherlands
BF	Burkina Faso	**GN**	Guinea	**NO**	Norway
BG	Bulgaria	**GR**	Greece	**NZ**	New Zealand
BJ	Benin	**HU**	Hungary	**PL**	Poland
BR	Brazil	**IE**	Ireland	**PT**	Portugal
CA	Canada	**IT**	Italy	**RO**	Romania
CF	Central African Republic	**JP**	Japan	**RU**	Russian Federation
CG	Congo	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CH	Switzerland			**SE**	Sweden
CI	Côte d'Ivoire	**KR**	Republic of Korea	**SK**	Slovak Republic
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CS	Czechoslovakia	**LK**	Sri Lanka	**SU**	Soviet Union
CZ	Czech Republic	**LU**	Luxembourg	**TD**	Chad
DE	Germany	**MC**	Monaco	**TG**	Togo
DK	Denmark	**MG**	Madagascar	**UA**	Ukraine
ES	Spain	**ML**	Mali	**US**	United States of America

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/01083

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/55

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	Cardiovascular Drugs and Therapy, vol. 4, supplement 1, 1990, Kluwer Academic Publishers, (US), D. LEBREC: "Portal hypertension: serotonin and pathogenesis", pages 33-35, see the whole article	1-11
A	Hepatology, vol. 9, no. 2, February 1989, American Association for the Study of Liver Diseases, (US), R. MASTAI et al.: "Serotonin blockade in conscious, unrestrained cirrhotic dogs with portal hypertension", pages 265-268, see the whole article	1-11

-/-

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
04-09-1992	25. 01. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme Dagmar FRANK

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	British Journal of Pharmacology, vol. 89, no. 3, November 1986, The Gresham Press, (GB), S.A. CUMMINGS et al.: "Hypersensitivity of mesenteric veins to 5-hydroxytryptamine- and ketanserin-induced reduction of portal pressure in portal hypertensive rats", pages 501-513, see the whole article	1-11
A	The American Journal of Surgery, vol. 160, no. 1, July 1990, (US), D. LEBREC: "Current status and future goals of the pharmacologic reduction of portal hypertension", pages 19-25, see the whole article	1-11
A	Gastroenterology, vol. 94, no. 5, part 2, May 1988, 89th Annual Meeting of the American Gastroenterological Association, New Orleans, Louisiana, 14-20 May 1988, H.S. ORMSBEE, III et al.: "SK&F103829 is a selective partial agonist at serotonergic 5-HT2 receptors, evaluation in functional receptor assays", page A336, see the whole abstract	1-11
A	Drug Development and Industrial Pharmacy, vol. 15, no. 4, 1989, Marcel Dekker, Inc., N. RAJAGOPALAN et al.: "Solubility properties of the serotonergic agonist 2,3,4,5-tetrahydro-8-(methylsulfonyl)-1H-3-benzazepin-7-ol", pages 489-497, see abstract; page 490: "Introduction"	1-11
X	EP,A,0229510 (SMITHKLINE BEECHAM) 22 July 1987, see abstract; page 2 - page 4, line 41 (cited in the application)	6-8
A	Clin. Physiol. Biochem., vol. 8, supplement 3, 1990, S. Karger AG, (Basel, DE), P.A. VAN ZWIETEN et al.: "Pathophysiological and pharmacotherapeutic aspects of serotonin and serotonergic drugs", pages 1-18, see page 6, column 1, line 37 - column 2, line 30; page 12, column 1, line 29 - column 2, line 17	1-5,12

-/-

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	Australian and New Zealand Journal of Medicine, vol. 19, no. 5, supplement 1, 1989, P.J. GOADSBY et al.: "Preliminary results for the use of GR43175, a new SHT1 receptor agonist, in the treatment of acute migraine", page 615, see the whole document	1-5,12
A	Recenti Progressi in Medicina, vol. 80, no. 12, December 1989, J.W. LANCE: "Headache: classification, mechanism and principles of therapy, with particular reference to migraine", pages 673-680, see page 673: "Summary"; page 676, column 2 - page 677, column 1; page 678, column 2	1-5,12
A	Australian and New Zealand Journal of Medicine, vol. 18, no. 3, 1988, J.W. LANCE: "Fifty years of migraine research", pages 311-317, see page 312, column 1 - page 313, column 1; page 316, paragraph 1	1-5,12
A	La Revue du Praticien, vol. 40, no. 5, 11 February 1990, (Paris, FR), P.-J. GOADSBY et al.: "Physiopathologie de la migraine", pages 389-393, see page 391, column 1	1-5,12

INTERNATIONAL SEARCH REPORT

In ational application No.
PCT/GB92/01083

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

FOR FURTHER INFORMATION PLEASE SEE FORM PCT/ISA/206 SENT TO YOU 30.09.92.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9201083 SA 60615

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 06/01/93
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0229510	22-07-87	US-A- 4659706	21-04-87
		AU-B- 589240	05-10-89
		AU-A- 6677986	25-06-87
		CA-A- 1263384	28-11-89
		JP-A- 62158255	14-07-87
		US-A- 4824839	25-04-89

EPO FORM P079

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:
A61K 31/55	A2	WO 93/00094
		(43) International Publication Date: 7 January 1993 (07.01.93)

(21) International Application Number: PCT/GB92/01083

(22) International Filing Date: 17 June 1992 (17.06.92)

(30) Priority data:

9113379.3	21 June 1991 (21.06.91)	GB
9113377.7	21 June 1991 (21.06.91)	GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)* : WARD, John, Gerard [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). YOUNG, Rodney, Christopher [GB/GB]; SmithKline Beecham Pharmaceuticals, The Fryth, Welwyn, Hertfordshire AL 6 9AR (GB). KAUMANN, Alberto, Julio [AR/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB).

(74) Agents: FLORENCE, Julia, A. et al.; Corporate Patents, SmithKline Beecham, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).

(81) Designated States: AU, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: MEDICAMENTS

(57) Abstract

Tetrahydrobenzazepine derivatives are disclosed as medicaments.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	ML	Mali
AU	Australia	FR	France	MN	Mongolia
BB	Barbados	GA	Gabon	MR	Mauritania
BE	Belgium	GB	United Kingdom	MW	Malawi
BF	Burkina Faso	GN	Guinea	NL	Netherlands
BG	Bulgaria	GR	Greece	NO	Norway
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	RO	Romania
CA	Canada	IT	Italy	RU	Russian Federation
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland			SN	Senegal
CI	Côte d'Ivoire	KR	Republic of Korea	SU	Soviet Union
CM	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TG	Togo
DE	Germany	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		
ES	Spain	MG	Madagascar		

MEDICAMENTS

The present invention relates to certain tetrahydrobenzazepine derivatives for use in the treatment of disorders characterised by excessive vasodilatation, in particular the treatment of portal hypertension and the treatment and prophylaxis of migraine, and more generally to the use of 5-HT_2 and 5-HT_1-like receptor agonists in the treatment of portal hypertension and to the use of 5-HT_2 agonists in the treatment and prophylaxis of migraine.

Portal hypertension, which is commonly associated with cirrhosis of the liver is characterised by increased portal venous blood flow, (which is caused by dilatation of mesenteric arterioles), and increased portal vascular resistance. A serious complication of this condition is rupture of esophageal varices or paraesophageal collaterals, which develop to reduce portal pressure.

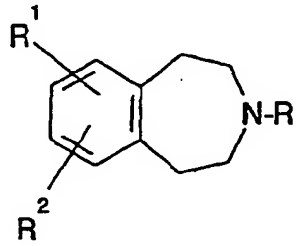
It has now been found that certain tetrahydrobenzazepines known in the art for the treatment of gastrointestinal motility disorders are agonists at 5-HT_2 and/or 5-HT_1-like-receptors and are expected to have utility in the treatment of portal hypertension.

Migraine is a non-lethal disease suffered by one in ten individuals. The main symptom is headache; other symptoms include vomiting and photophobia. Currently, the most widely used treatment for migraine involves administration of ergotamine, dihydroergotamine or methysergide. All these drugs are inter alia agonists of $5HT_1$-like receptors but also have other actions; treatment with them is associated with a number of adverse side effects. In addition, some patients experience a "withdrawal headache" following the cessation of treatment with an ergot product, such as ergotamine, causing them to repeat the treatment and resulting in a form of addiction.

In view of the foregoing, there is clearly a need for the provision of effective and safe medicaments for the treatment of migraine.

It has now been found that certain tetrahydrobenzazepines known in the art for the treatment of gastrointestinal motility disorders are agonists at $5HT_1$-like and/or $5HT_2$-receptors and are expected to have utility in the treatment of migraine.

The present invention therefore provides compounds of structure (I):



Structure (I)

in which:
R is hydrogen, C_{1-6}alkyl or C_{3-5}alkenyl;
R^1 is NO_2, cyano, halo, COR^3, SO_nR^4 or $SO_nNR^5R^6$;
R^2 is hydrogen, hydroxy or C_{1-4}alkoxy;
R^3 is hydrogen, C_{1-4}alkyl, OR^5 or NR^5R^6;
R^4 is C_{1-6}alkyl or halo C_{1-6} alkyl;
R^5 and R^6 are hydrogen, C_{1-6}alkyl or C_{3-6} cycloalkyl; and n is 1 or 2;
and pharmaceutically acceptable salts thereof for use in the manufacture of a medicament for the treatment of portal hypertension and/or migraine.

Suitably R is hydrogen, C_{1-6}alkyl or C_{3-5}alkenyl; preferably R is hydrogen.

Suitably R^1 is nitro, cyano, halo, COR^3, SO_nR^4 or $SO_nNR^5R^6$; preferably R^1 is SO_nR^4, nitro or halo; most preferably R^1 is SO_nR^4.

Suitably n is 1 or 2; preferably n is 2.

Suitably R^2 is hydrogen, hydroxy or C_{1-4}alkoxy; preferably R^2 is C_{1-4}alkoxy or hydroxy.

Suitably R^3 is hydrogen, C_{1-4}alkyl, OR^5 or NR^5R^6; preferably R^3 is C_{1-4}alkyl, in particular methyl.

Preferably the group R^1 is at the 8-position and the group R^2 is at the 7-position of the ring of the compound of structure (I).

Suitably R^4 is C_{1-6}alkyl or halo C_{1-6} alkyl; preferably R^4 is C_{1-6}alkyl, or C_{1-6} alkyl substituted by 1 to 6 halogen atoms (eg. CF_3). and most preferably R^4 is methyl.

Suitably R^5 and R^6 are hydrogen or C_{1-6}alkyl, or C_{3-6} cycloalkyl. Preferably, when both groups represent C_{1-6} alkyl, they are the same.

C_{1-6}alkyl groups, either alone or as part of another group, can be straight or branched.

Suitable salts will be apparent to those skilled in the art, and include, for example, acid addition salts such as the hydrochloride, or the oxalate.

Suitable examples of compounds for use in the present invention are as described in EP-0229510-B, for example :

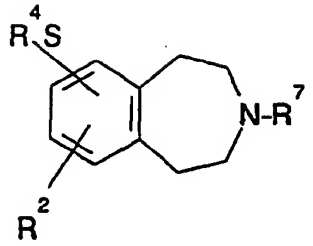
7-hydroxy-8-sulphamoyl-2,3,4,5-tetrahydro-1H-benzazepine, and 7-hydroxy-8-(N,N-dimethylsulphamoyl)-2,3,4,5-tetrahydro-1H-benzazepine.

In particular the present invention relates to the use of a compound in which R is hydrogen, R^1 is methylsulphonyl and R^2 is hydroxy, namely, 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of migraine.

Certain compounds falling within the scope of structure (I) are themselves novel and as such form a further aspect of the invention. These compounds are in particular:
7-methoxy-8-methylsulphinyl-2,3,4,5-tetrahydro-1H-benzazepine oxalate;
7-methoxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride;
7-hydroxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride;
7-methoxy-8-bromo-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride;
7-hydroxy-8-bromo-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride;
7-methoxy-6-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride;
6-bromo-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride;
8-acetyl-7-hydroxy-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride;
7-hydroxy-8-methylsulphinyl-2,3,4,5-tetrahydro-1H-benzazepine; and
7-hydroxy-8-trifluoromethylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine.

Compounds of structure (I) may be prepared by the methods described in EP 0229510-B, or by the following methods :

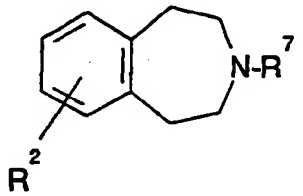
a) to prepare a compound of structure (I) where R^1 represents $-SO_nR^4$, the reaction of a compound of structure (II) :



Structure (II)

(wherein R^2 and R^4 are as hereinbefore defined and R^7 is an N-protecting group) with an oxidising agent, in the presence of titanium trichloride;

b) to prepare a compound of structure (I) wherein R^1 represents $-COR^3$, NO_2 or halogen, the reaction of a compound of structure (III) :



Structure (III)

(wherein R^2, R^3 and R^7 are as hereinbefore defined) with an appropriate acylating, nitrating or halogenating agent respectively; followed in each case by removal of the N-protecting group, and if desired salt formation.

Suitable N-protecting groups R^7 are well known in the art and include acyl groups such as acetyl, trifluoroacetyl, benzoyl, methoxycarbonyl, and benzyloxycarbonyl. N-deprotection may be carried out by conventional methods.

In process (a) the oxidising agent may be for example hydrogen peroxide or a peracid such as 3-chloroperbenzoic acid, in a solvent such as acetic acid. It will be

appreciated that one equivalent of the oxidising agent will produce a compound wherein n is 1 and two or more equivalents will give a compound wherein n is 2.

In process (b) the acylating agent may be for example an acid chloride or acid anhydride corresponding to the group R^3CO-. The reaction is desirably effected in the presence of tin tetrachloride. Nitration may be effected using concentrated nitric acid in admixture with acetic anhydride, followed by neutralisation with e.g. sodium bicarbonate. Halogenation may be carried out with an acidic solution of a halogen e.g. Br_2 in acetic acid, followed by neutralisation with e.g. sodium bicarbonate. In general the nitration and halogenation reactions will result in a mixture of isomeric compounds, substituted respectively at the 7,8 and 6,7 positions of the benzazepine ring, which may be separated for example by chromatography, or crystallisation.

The compounds of structure (I) have been found to be agonists at 5-HT_2 and/or 5-HT_1-like receptors and are expected to have utility in medicine in the treatment or prophylaxis of portal hypertension. Whilst not wishing to be bound by theory, it is believed that 5-HT_1-like agonists and 5-HT_2-agonists are effective in portal hypertension through constriction of mesenteric arterioles, and partial constriction of paraesophageal collaterals with consequent reduction of portal flow and portal pressure. Preferred compounds for use according to the present invention are partial agonists at 5-HT_2 receptors and/or 5-HT_1-like receptors.

It is believed that the use of 5-HT_2 and 5-HT_1-like-receptor agonists in the treatment of portal hypertension has not previously beeen described and hence represents a novel use for these classes of compounds.In a further aspect therefore the present invention provides 5-HT_2 receptor agonists and 5-HT_1-like-agonists for use in the treatment of portal hypertension. The invention also provides the use of 5-HT_2 receptor agonists and 5-HT_1-like-agonists in the manufacture of a medicament for the treatment of portal

hypertension. Also provided is a method of treating portal hypertension which comprises administering to a subject in need thereof an effective amount of a 5-HT_2-agonist or 5-HT_1-like-agonist. For use according to the present invention a 5-HT_2-agonist or 5-HT_1-like-agonist is preferably a partial agonist at the said receptor. Most preferably, a compound for use according to this invention is a partial agonist at both 5-HT_2 and 5-HT_1-like receptors.

The compounds of structure (I) have been found to be agonists at $5HT_1$-like and/or $5HT_2$ receptors and are expected to have utility in medicine in the treatment or prophylaxis of migraine. Whilst not wishing to be bound by theory, it is believed that $5HT_1$-like agonists are effective in migraine through constriction of cerebral arteries and that $5HT_2$ agonists constrict the superficial temporal artery. Preferred compounds for use according to the present invention are partial agonists at $5HT_1$-like and/or $5HT_2$ receptors.

It is believed that the use of 5-HT_2-receptor agonists in the treatment of migraine has not previously been described and hence represents a novel use for this class of compound. In a further aspect therefore the present invention provides 5-HT_2-receptor agonists for use in the treatment of migraine. The invention also provides the use of 5-HT_2-receptor agonists in the manufacture of a medicament for the treatment of migraine. Also provided is a method of treating migraine which comprises administering to a subject in need thereof an effective amount of a 5-HT_2 agonist. For use according to the present invention a 5-HT_2-agonist is preferably a partial agonist at this receptor.

In therapeutic use the compounds are incorporated into standard pharmaceutical compositions. They can be administered orally, parenterally, rectally or transdermally.

The compounds of structure (I) and their pharmaceutically acceptable salts which are active when given

orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

The compounds of structure (I) and their pharmaceutically acceptable salts which are active when administered parenterally (i.e. by injection or infusion) can be formulated as solutions or suspensions.

A composition for parenteral administration will generally consist of a solution or suspension of the active ingredient in a sterile aqueous carrier or parenterally acceptable oil, for example polyethyleneglycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

A typical suppository composition comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

A typical transdermal formulation comprises a conventional aqueous or non-aqueous vehicle, for example, a cream, ointment lotion or paste or in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dose form. Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 150 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 1000 mg, preferably between 1 mg and 400 mg, for example between 10 and 400 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 30 mg, for example between 1 and 30 mg of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy.

BIOLOGICAL DATA

5-HT_1-like Receptor Screen

Dog Saphenous Vein

Helicoids of dog saphenous vein were set up at 37°C in modified Krebs solution at a resting force of 10 mN. The solution also contained 1 µmol/l each of ketanserin prazosin, atropine and mepyramine, 6 µmol/l cocaine and 200 µmol/l ascorbate. Nearly isomeric contractions were measured with force transducers on a polygraph. The tissues were exposed twice to 5-hydroxytryptamine (5-HT) 2 µmol/l followed by washes. A cumulative concentration-effect curve to the test compound was determined, followed by a curve to 5-HT in the presence of the highest used concentration of test compound. Contractions caused by the test compound were compared with those caused by 5-HT. The intrinsic activity of the test compound was calculated as the ratio of the maximum test compound-induced effect over the effect caused by 2 µmol/l 5-HT. The EC_{50} of the test compound was estimated from the corresponding effect curve. When appropriate equilibrium dissociation constraints Kp were estimated by the method of Marano & Kaumann (1976, J. Pharmacol. Exp. Ther. 198, 518-525).

The compounds of structure (I) have been found to demonstrate activity in this screen, for example: 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine (prepared according to the procedures described in EP 229510-B), was found to have an EC_{50} of 0.2 µM, and the compound of Example 1 an EC_{50} of 20 µM.

RABBIT BASILAR ARTERY

METHODS

Experiments were performed in intracranial arteries from rabbit isolated basilar artery in a similar method to

one described previously (Parsons and Whalley, 1989. Eur J Pharmacol 174, 189-196.).

In brief, rabbits were killed by overdose with anaesthetic (sodium pentobarbitone). The whole brain was quickly removed and immersed in ice cold modified Kreb's solution and the basilar artery removed with the aid of a dissecting microscope. The Krebs solution was of the following composition (mM) Na^+ (120); K^+ (5); Ca^{2+} (2.25); Mg^{2+} (0.5); Cl^- (98.5); SO_4^{2-} (1); EDTA (0.04), equilibrated with 95% O_2/5% CO_2. The endothelium was removed by a gentle rubbing of the lumen with a fine metal wire. Arteries were then cut into ring segments (ca 4-5 mm wide) and set up for recording of isometric tension in 50 ml tissue baths in modified Krebs solution with the additional supplement of (mM); Na^{2+} (20); fumarate (10); pyruvate (5); L-glutamate (5) and glucose (10). The arteries were then placed under a resting force of 3-4 mN maintained at 37°C and the solution bubbled with 95% O_2/5% CO_2.

After tests for initial reactivity with 90 mM KCl depolarising solution and for lack of acetylcholine-induced relaxation of 5-HT (10 mM) precontraction, cumulative concentration-effect curves (2 nM-60 mM) to 5-HT were constructed in the presence of ascorbate 200 mM, cocaine 6 mM, indomethacin 2.8 mM, ketanserin 1 mM and prazosin 1 mM.

Following a 45-60 min wash period, cumulative concentration-effect curves to the test compounds or 5-HT (as a time match control) were constructed in the presence of ascorbate, indomethacin, cocaine, ketanserin and prazosin.

5-HT_2-Receptor Screen

Rat Tail Artery (Kaumann A.J. & Frenken M. 1988, J. Pharmacol. Exp. Pharmacol. 245, 1010-1015)

The ventral caudal artery was used from rats pretreated with reserpine 7mg/kg ip (20 h). Five interconnected arterial rings were prepared and set up to contract in

modified Krebs solution at 32.5°C as follows. Resting force of the rings was set to be 4 mN and the rings allowed to relax thereafter without further readjustment. Three cumulative concentration-effect curves were determined, the first to 5-HT followed by washout, the second to the test compound and the third to 5-HT in the presence of the highest used concentration of test compound. The intrinsic activity of the test compound was calculated as the ratio of the maximum test compound-induced effect over maximum 5-HT-induced effect. The EC_{50} of the test compound was estimated from the corresponding concentration-effect curve. Equilibrium dissociation constants Kp were estimated by the method of Marano & Kaumann (1976, J. Pharmacol. Exp. Ther., 198, 518-525).

The compounds of structure (I) have been found to demonstrate activity in this screen, for example, 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H- benzazepine was found to have an EC_{50} of 2 μM, and the compound of Example 2 an EC_{50} of 1 μM.

Portal Hypertension - In vivo

The effect of 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine was investigated on superior mesenteric arterial flow in conscious normal and portal vein-ligated rats (Sprague-Dawley). Portal hypertension in portal vein-ligated rats was produced as described (Groszmann et al. 1982). A Doppler flowmeter probe was implanted into the superior mesenteric artery for chronic studies. Superior mesenteric flow changes were observed during 4 days, followed by 4 days' exposure to 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine in the drinking water and another period of 4 days without 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine in the drinking water. 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine significantly reduced superior mesenteric flow in both sham-operated and portal vein-ligated rats. The effect was reversible during the last 4 day period without 7-hydroxy-8-

methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine in the drinking water.

Groszmann R J, Vorobioff J and Riley E (1982). Splachnic hemodynamics in portal hypertensive rats: measurement with gamma-labelled microspheres. Am J Physiol 242: G156-G160.

PHARMACEUTICAL FORMULATIONS

1. **Formulation for intravenous infusion**

Compound of structure (I)	0.1 - 150 mg
Sodium hydroxide/hydrochloric acid	to pH ca 7
polyethylene glycol	0 - 30 ml
propylene glycol	0 - 30 ml
alcohol	0 - 10 ml
water	to 100 ml

2. **Formulation for bolus injection**

Compound of structure (I)	0.1 - 150 mg
sodium hydroxide or hydrochloric acid	to pH ca 7
polyethylene glycol	0 - 2.5 ml
alcohol	0 - 2.5 ml
water	to 5 ml

A toxicity adjusting agent eg. sodium chloride, dextrose or mannitol may also be added.

3. **Tablet for oral administration**

	mg/tablet
Compound of structure (I)	50
lacatose	153
starch	33
crospovidone	12
microcrystalline cellulose	30
magnesium stearate	2
	280

Examples

Compounds within the scope of the present invention (e.g. 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-3-benzazepine) can be prepared using the methods described in EP-229510-B or the methods disclosed hereinbefore.

Example 1

7-Methoxy-8-methylsulphinyl-,3,4,5-tetrahydro-1H-benzazepine monooxalate

3-Acetyl-7-methoxy-8-methylthio-2,3,4,5-tetrahydro-1H-benzazepine (3.04g) was dissolved in methanol (500 ml) and treated with a 15% solution of titanium trichloride (11.8g), followed by 6% hydrogen peroxide solution (18.0g), dropwise, with stirring, over 10 minutes at room temperature. After stirring for a further 30 minutes, the reaction mixture was filtered, diluted with water and extracted with chloroform. The latter extract was washed with aqueous sodium sulphite, then water, dried, filtered, and evaporated to dryness leaving 3-acetyl-7-methoxy-8-methylsulphinyl-,3,4,5-tetrahydro-1H-benzazepine (3.21g) as a solid, m.p. 130-2°C.

The above product (20mg) was hydrolyzed by refluxing a solution in isopropanol (1ml) with 40% aqueous sodium hydroxide (1ml) for 60 hours. Most of the isopropanol was evaporated in vacuo, and the remaining solution was diluted with water, and extracted with chloroform. The extracts were combined, dried ($MgSO_4$) and evaporated to give 7-methoxy-8-methylsulphinyl-,3,4,5-tetrahydro-1H-benzazepine (17mg) which was converted to the monooxalate salt, m.p. 212-4°C.

Example 2

7-Methoxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride

Concentrated nitric acid (0.6ml, 70% w/w) was added to a stirred, ice-cooled solution of 3-acetyl-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine (1.98g) in acetic anhydride (30ml) over 5-6 hours. The solution was allowed to warm to room temperature and, after standing overnight, was added to saturated aqueous sodium bicarbonate. When all of the excess acetic anhydride had reacted, the resulting mixture was saturated with sodium chloride and extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated to a gum, which was purified by chromatography (SiO_2; C_6H_{14}/EtOAc) to give 3-acetyl-7-methoxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine (0.93g), m.p. 127-132°C, and 3-acetyl-6-nitro-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine which was recrystallised from benzene (0.16g), m.p. 143-149°C.

The above product (3-acetyl-7-methoxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine) (0.90g) was heated at reflux in 3N.HCl (54ml) for 16 hours. The resulting solution was evaporated to dryness to leave a yellow solid which was triturated with acetone and collected by filtration. The beige solid thus obtained was dried over P_2O_5 and recrystallised from methanol to give 7-methoxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride (0.74g), m.p. 234-7°C.

Example 3

7-Hydroxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride

7-Methoxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride (0.40g) was dissolved in 48% aqueous hydrobromic acid, and the solution was heated to reflux for 24 hours. The solution was evaporated to dryness to leave a

crude yellow solid which was basified and purified by chromatography (SiO_2; $CHCl_3$/MeOH), then recrystallised from methanol/conc. hydrochloric acid to give 7-hydroxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride (0.11g), m.p. 251-5°C.

Example 4

7-Methoxy-8-bromo-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride

3-Acetyl-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine (5.0g) was dissolved in glacial acetic acid (70ml) and heated to 70°C. A 1.0M solution of bromine in acetic acid was added over 20-30 minutes, and the resulting solution was heated at 70°C for a further hour. The solution was allowed to cool overnight, during which a mass of beige crystals was obtained. These were collected by filtration, basified and purified by chromatography (SiO_2; CH_2Cl_2/EtOAc), followed by crystallisation from ethyl acetate/ether to give 3-acetyl-7-methoxy-8-bromo-2,3,4,5-tetrahydro-1H-benzazepine (1.55g), m.p. 123-125°C, and 3-acetyl-6-bromo-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine, m.p. 99-101°C.

The above product (3-acetyl-7-methoxy-8-bromo-2,3,4,5-tetrahydro-1H-benzazepine) (0.30g) was heated under reflux in 3M HCl (16.5ml) for 20 hours. The solution was evaporated to dryness in vacuo and triturated with acetone to give 7-bromo-8-methoxy-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride as a white solid (0.25g), m.p. 268-272°C.

Example 5

7-Hydroxy-8-bromo-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride

A solution of 3-acetyl-7-methoxy-8-bromo-2,3,4,5-tetrahydro-1H-benzazepine (0.5 g) in dichloromethane (12 ml) was cooled in an acetone/dry ice bath. Boron tribromide

(0.32 ml) was added to the stirred solution in one portion, and the mixture was allowed to warm to room temperature over 1 hour. Stirring was continued for a further 30 minutes, then water was added. The mixture was partitioned between water and dichloromethane, and the aqueous layer was re-extracted with dichloro-methane. The combined extracts were washed with water and brine, dried ($MgSO_4$) and evaporated to a solid, which was purified by chromatography (SiO_2; $CHCl_3$/MeOH) to give 3-acetyl-7-hydroxy-8-bromo -2,3,4,5-tetrahydro-1H-benzazepine as a white solid (0.37 g).

The above product (0.30 g) was heated in 3N HCl (50 ml) to reflux overnight. The resulting solution was evaporated to dryness and triturated with acetone to give a white solid. This was recrystallised from n-propanol/ HCl to give the title compound as white crystals (0.21 g), m.p. 277-281°C.

Example 6

7-Methoxy-6-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride

The title compound was prepared following the procedures described in Example 2, by heating 3-acetyl-7-methoxy-6-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride (0.15g) in 3N.HCl (9mL) at reflux. The product, 7-methoxy-6-nitro-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride, was isolated as described, and recrystallised from n-propanol to give small yellow crystals (0.077g), m.p. 258-61°C decomp.

Example 7

6-Bromo-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride

The title compound was prepared following the procedures described in Example 2, by heating 3-acetyl-6-bromo-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine (0.20g) in 3N.HCl (11 mL) at reflux. The product, 6-bromo-7-methoxy-

2,3,4,5-tetrahydro-1H-benzazepine hydrochloride, was isolated as described and recrystallised from n-propanol to give white needles (0.12g), m.p. 255-60°C.

Example 8

8-Acetyl-7-hydroxy-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride

Tin tetrachloride (2.4 mL) was added dropwise, with stirring to a solution of acetyl chloride (1.46 mL) in CH_2Cl_2 (15 mL), at room temperature. Stirring was continued for a further 1 hour, and then a solution of 7-methoxy-3-acetyl-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride (3.0g) in CH_2Cl_2 (15 mL) was added over a period of 20 minutes. The mixture was left to stir for 16 hours, and then partitioned between 3N.HCl and CH_2Cl_2. The aqueous layer was re-extracted and the combined organic layers were washed with saturated sodium bicarbonate solution and then H_2O, dried ($MgSO_4$) and evaporated. The residue was dissolved in methanol and treated with charcoal. The filtrate was evaporated to dryness and the residue extracted twice with boiling benzene, the extracts decanted combined and evaporated to give a solid which was triturated with ether. The product, 3,8-diacetyl-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine, was obtained as an off-white solid (1.7g), m.p. 142-6°C.

The 3,8-diacetyl-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine (0.20g) was dissolved in CH_2Cl_2 (5 mL) and cooled to ca -70°C (acetone/solid CO_2 bath). Boron trichloride (1.0M solution in CH_2Cl_2; 1.53 mL) was added from a syringe over 10 minutes. The mixture was allowed to warm slowly to room temperature (1 hour) and then stirred for a further 30 minutes. The reaction was quenched by the addition of H_2O and the mixture was partitioned between water and CH_2Cl_2. The aqueous layer was re-extracted with CH_2Cl_2 and the combined organic layers washed with water and brine, and dried ($MgSO_4$). Evaporation gave a gum which was purified by flash chromatography (SiO_2; $CHCl_3$/MeOH). The product, 3,8-

diacetyl-7-hydroxy-2,3,4,5-tetrahydro-1H-benzazepine, crystallised from ether as an off-white solid (0.129g), m.p. 131-4°C.

The above diacetyl compound (0.121g) was heated at reflux in 3M.HCl (3.7 mL) for 16 hours. The solution was then evaporated to dryness, giving a yellow-orange crystalline solid. This was recrystallised from n-propanol containing dissolved HCl gas, to yield the product, 8-acetyl-7-hydroxy-2,3,4,5-tetrahydro-1H-benzazepine hydrochloride, as small orange crystals (0.064g), m.p. 241-7°C decomp.

Example 9

7-Hydroxy-8-methylsulphinyl-2,3,4,5-tetrahydro-1H-benzazepine

Aluminium chloride (1.71 g) was added to dichloromethane (50 ml) at room temperature, and a solution of 3-acetyl-7-methoxy-8-methylsulphinyl-2,3,4,5-tetrahydro-1H-benzazepine (0.90 g) in dichloromethane was added dropwise with stirring over 3h. After leaving the mixture to stir overnight at room temperature, the dichloromethane solution was decanted from the precipitated gum. The latter was digested with 1M sodium hydroxide solution, and the resulting aqueous solution was washed with dichloromethane, acidified to pH_2 with conc. HCl and extracted (3x) with chloroform. The extract was dried ($MgSO_4$), evaporated to an oil, and purified by chromatography (SiO_2; $MeOH/CH_2Cl_2$) to give 3-acetyl-7-hydroxy-8-methylsulphinyl-2,3,4,5-tetrahydro-1H-benzazepine (0.72 g).

The above product (0.64 g) was heated with 1M sodium hydroxide solution (10 ml) at 100°C overnight. After cooling, the mixture was passed down an ion exchange column (Amberlite CG50; NH_4^+) and eluted with water. The resulting eluate was evaporated to dryness, extracted with hot methanol, treated with activated charcoal, filtered and

evaporated to a green gum. This crystallized on addition of acetonitrile to give the title compound (0.45 g), mp 175-8°C.

Example 10

7-Hydroxy-8-trifluoromethylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine

3-Acetyl-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine (7.0 g) was dissolved in dry dichloromethane (100 ml), cooled in an ice bath, and treated dropwise with chlorosulphonic acid (13.9 g), with stirring. The mixture was stirred for a further 2 1/2 h at room temperature and then poured carefully onto ice. The resulting brown oil was partitioned between dichloromethane and water, and the aqueous layer was extracted further with dichloromethane. Combined organic extracts were dried ($MgSO_4$) and evaporated to give 3-acetyl-7-methoxy-8-chlorosulphonyl-2,3,4,5-tetrahydro-1H-benzazepine (4.5 g).

The above product (3.95 g) was dissolved in acetic acid (75 ml), and stannous chloride dihydrate (11.2 g) and conc. HCl (15 ml) were added. The mixture was stirred at 75°C for 1 h then poured into ice water and shaken with ethyl acetate. The solid thus produced was combined with the ethyl acetate extracts and evaporated to dryness in vacuo. This crude product was shaken with dry ethanol (200 ml) and filtered. The resulting solid was stirred with 1M NaOH solution (100 ml) for 30 min., filtered, acidified with conc. HCl and extracted with chloroform. The extracts were combined, dried ($MgSO_4$) and evaporated to dryness to give 3-acetyl-7-methoxy-8-mercapto-2,3,4,5-tetrahydro-1H-benzazepine (1.86 g).

This product (1.22 g) was dissolved in dry DMF (50 ml) and potassium carbonate (1.33 g) added. Trifluoromethyl iodide was bubbled through the solution, while irradiating with U.V. light, with cooling, for 5 h. Most of the DMF was removed under vacuum, and the residue was partitioned between

chloroform and 1M NaOH solution. The organic phase was dried ($MgSO_4$) and evaporated to dryness. The residue was purified by chromatography (SiO_2; $CHCl_3$/MeOH) to give 3-acetyl-7-methoxy-8-trifluoromethyl-2,3,4,5-tetrahydro-1H-benzazepine (0.33 g).

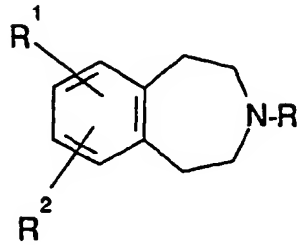
The above product (1.0 g) was dissolved in 1,2-dichloro-ethane (75 ml) and meta-chloro perbenzoic acid (2.26 g) was added. The mixture was heated under reflux for 2 h. The resulting cooled solution was washed with 1M NaOH solution, dried ($MgSO_4$) and evaporated to dryness leaving 3-acetyl-7-methoxy-8-trifluoromethylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine (0.95 g).

This product (0.50 g) was dissolved in dichloromethane (100 ml) and boron tribromide (0.71 g) was added dropwise with stirring at room temperature overnight. Methanol was added cautiously, dropwise, and the solvents were removed in vacuo. The residual green oil consisting of the 7-hydroxy compound was dissolved in chloroform and washed with 1M NaOH solution.

The aqueous phase was separated and heated at 100°C for 40 h, cooled, and passed down an ion exchange column (Amberlite CG-50(H). The relevant fractions were combined and evaporated to dryness to leave a residue which was chromatographed (SiO_2; $CHCl_3$/MeOH/MH_4OH) to give a product which was crystallized under acetonitrile to give the title compound (0.12 g), mp >273°C.

CLAIMS:

1. The use of a compound of structure (I)



Structure (I)

in which:
R is hydrogen, C_{1-6}alkyl or C_{3-5}alkenyl;
R^1 is NO_2, cyano, halo, COR^3, SO_nR^4 or $SO_nNR^5R^6$;
R^2 is hydrogen, hydroxy or C_{1-4}alkoxy;
R^3 is hydrogen, C_{1-4}alkyl, OR^5 or NR^5R^6;
R^4 is C_{1-6}alkyl or halo C_{1-6}alkyl;
R^5 and R^6 are hydrogen or C_{1-6}alkyl or C_{3-6} cycloalkyl; and
n is 1 or 2;
or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of portal hypertension and/or migraine.

2. The use of a compound according to claim 1 in which R^1 is at the 8-position and R^2 is at the 7-position of the ring of the compound of structure (I).

3. The use of a compound according to claim 1 or claim 2 in which R^1 is SO_2R^3, R^2 is hydrogen, alkoxy or hydroxy and R is hydrogen.

4. The use of a compound according to any of claims 1 to 3 in which R^3 is methyl and R^2 is hydroxy.

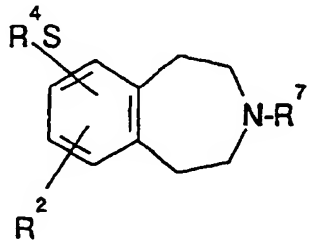
5. The use of a compound according to claim 1 which is 7-hydroxy-8-methylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine.

6. A compound according to claim 1 which is:
7-methoxy-8-methylsulphinyl-,3,4,5-tetrahydro-1H-benzazepine;
7-methoxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine;
7-hydroxy-8-nitro-2,3,4,5-tetrahydro-1H-benzazepine;
7-methoxy-8-bromo-2,3,4,5-tetrahydro-1H-benzazepine;
7-bromo-8-hydroxy-2,3,4,5-tetrahydro-1H-benzazepine;
7-methoxy-6-nitro-2,3,4,5-tetrahydro-1H-benzazepine;
6-bromo-7-methoxy-2,3,4,5-tetrahydro-1H-benzazepine;
8-acetyl-7-hydroxy-2,3,4,5-tetrahydro-1H-benzazepine;
7-hydroxy-8-methylsulphinyl-2,3,4,5-tetrahydro-1H-benzazepine; and
7-hydroxy-8-trifluoromethylsulphonyl-2,3,4,5-tetrahydro-1H-benzazepine;
or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising a compound according to claim 6 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or excipient therefor.

8. A process for preparing a compound of Structure (I) wherein R, R^2, R^3, R^4, R^5 and n are as defined in claim 1 and R^1 represents SO_nR^4, $-COR^3$, NO_2 or halogen, which comprises :

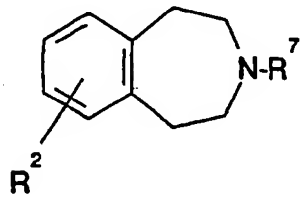
a) to prepare a compound of structure (I) where R^1 represents $-SO_nR^4$, the reaction of a compound of structure (II) :



Structure (II)

(wherein R^2 and R^4 are as hereinbefore defined and R^7 is an N-protecting group) with an oxidising agent, in the presence of titanium trichloride;

b) to prepare a compound of structure (I) wherein R^1 represents $-COR^3$, NO_2 or halogen, the reaction of a compound of structure (III) :



Structure (III)

wherein R^2, R^3 and R^7 are as hereinbefore defined) with an appropriate acylating, nitrating or halogenating agent respectively; followed in each case by removal of the N-protecting group, and if desired salt formation.

9. Use of a 5-HT_2 receptor agonist in the treatment of portal hypertension.

10. Use of a 5-HT_1-like-receptor agonist in the treatment of portal hypertension.

11. Use of a compound which is an agonist at both 5-HT_2 and 5-HT_1-like-receptors in the treatment of portal hypertension.

12. Use of a 5-HT_2 receptor agonist in the treatment and prophylaxis of migraine.